The Dow Chemical Company
Midland, MI 48674
USA

715 East Main Street
April 23, 2015

CONFIDENTIAL BUSINESS INFORMATION 40 CFR 2.201-2.215

VIA CDX

Document Processing Center (7407M)
(Attn: TSCA Section 8(e) Coordinator)
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
1201 Constitution Avenue, NW
Washington, DC 20004-3302

Generic Name: Bis-Heterocyclic Amide

The following information is being submitted by The Dow Chemical Company (Dow) pursuant to current guidance issued by EPA indicating EPA's interpretation of Section 8(e) of the Toxic Substances Control Act. Dow has made no determination as to whether a significant risk of injury to health or the environment is actually presented by the findings.

Ten male and ten female Fisher 344/DuCrl rats per group were given test diets containing of the test substance at concentrations of 0, 30, 150, or 750 ppm for at least 90 days, which corresponded to time-weighted average doses of 0, 1.79, 8.95 or 44.7 milligrams of the test substance per kilogram body weight per day (mg/kg/day) for males and 0, 1.98, 9.92, or 49.8 mg/kg/day for females, respectively. Additional groups of 10 male and 10 female rats given 0 or 750 ppm for the 90-day treatment period were switched to control feed for another 28 days to evaluate recovery from potential treatment-related effects.

Clinical Pathology

Males and females given 750 ppm had treatment-related, decreased red blood cell counts, hemoglobin levels, and hematocrits (approximately 4-6 %, 4-5%, 3-4%, respectively) compared to controls. These changes were accompanied by higher reticulocyte and platelet counts and a slightly higher mean corpuscular volume (females only) as compared to respective controls, consistent with a regenerative response of the hematopoietic system to the decreased red cell mass. A very slight increase in erythrocytic polychromasia was noted in peripheral blood smears of both sexes at 750 ppm consistent with the higher reticulocyte counts. Methemoglobin concentrations were marginally higher than controls and statistically significant in all male and female treatment groups. The higher methemoglobin concentrations in males and females at 30 or 150 ppm were interpreted to be non-adverse due to the

animal difference from the control and lack of any associated hematological changes.

Organ Weights and Histopathology

Treatment-related organ weight changes were observed in the liver, spleen, thyroid gland, and kidneys in the 750 ppm dose-group. Absolute liver weights were increased 23.5% and 24.1% in males and females, respectively and relative liver weights were 24.6% higher in both sexes as compared to controls. Spleen weights (absolute) were increased 11.6% and 25.7%, and relative spleen weights were increased 12.4% and 26.8% in males and females, respectively. Thyroid gland weights were increased 15.7% and 23% (absolute) and 17.8% and 23.3% (relative), in males and females, respectively. Kidney weights were marginally increased by 3.9% and 6.3% (absolute), respectively) and 4.8% and 6.6% (relative) in males and females, respectively. Organ weight changes in other dose groups were limited to males given 150 ppm with increased absolute and relative liver weights (12.4% and 9.5%, respectively), and increased absolute and relative thyroid gland weights (10.4% and 8.9%, respectively), as compared to controls.

Treatment-related histopathological changes were observed in the liver, spleen, thyroid, bone marrow and the kidney. In the liver, corresponding to higher liver weights, males and females given 750 ppm had very slight panlobular hepatocyte hypertrophy with increased eosinophilia. In addition, females given 750 ppm had a very slight increase in the amount of pigment (consistent with bile) in occasional Kupffer cells, very slight increase in mitotic figures in hepatocytes and decreased incidence of vacuolization (consistent with fatty change) in the periportal hepatocytes. Males given 150 ppm had very slight centrilobular/midzonal hepatocyte hypertrophy with increased eosinophilia.

In the spleen, males and females given 750 ppm had very slight or slight diffuse congestion of the red pulp, very slight or slight increase in extramedullary erythrocytic hematopoiesis and very slight increase in amounts of pigment (hemosiderin) laden macrophages consistent with accelerated turnover of RBCs. A very slight or slight erythroid cell hyperplasia was also noted in the bone marrow in males and females given 750 ppm consistent with a regenerative response of the hematopoietic system to the decrements in red blood cell mass. In the thyroid gland, males given 750 ppm had treatment-related, very slight follicular cell hypertrophy. Although the weights were higher, there were no treatment-related histopathological changes in the thyroid of females given 750 ppm or in males given 150 ppm. In the kidneys of females given 750 ppm, there was a very slight increase in the amounts of a fine brown granular pigment (consistent with lipofuscin) within the tubular epithelial cells.

Immunotoxicity

Assessment of immunotoxicity as measured by antibody (IgM) response to intravenously administered sheep red blood cells(SRBCs) revealed a treatment-related decrease in the average antigen-specific IgM response in females given 750 ppm. There were no treatment-related effects in immune responsiveness of males given 750 or in males and females given 150 or 30 ppm. The observed decrease in the antibody response in females given 750 ppm was considered secondary to systemic toxicity as the test substance did not exhibit evidence of primary treatment-related immunotoxicity in response to SRBCs.

Conclusions

Treatment-related effects at 750 ppm consisted of alterations in hematology parameters including increased methemoglobin, and alterations in liver, spleen, thyroid, bone marrow, and kidney weights and/or histopathology. All treatment-related adverse effects observed at 750 ppm recovered by the end of the 28-day recovery period. Treatment-related effects observed at 150 ppm were all considered non-adverse. Therefore, the Lowest-Observed-Adverse Effect Level (LOAEL) of the test substance in Fisher 344 rats was determined to be 750 ppm, which corresponded to 44.7 and 49.8 mg/kg/day in males and females.

Questions may be addressed to the undersigned.

Sincerely,

Beth Lohrke-Stieve
PH: 989-638-1472
FAX: 989-638-9933
E-MAIL: blstieve@dow.com